Table II. Parental Smoking and Respiratory Health Effects in School Age Children

| Study | Asthma | Cough | Wheeze | Bronchitis | Other |
|---|---|---|---|---|---|
| Cameron et al., 1969[2] | | | | | +[1] |
| Colley, 1974 | | + | | | |
| Lebowitz & Burrows, 1976[2] | -[1] | - | - | - | - |
| Schilling et al., 1977 | - | - | +[3] | - | - |
| Said et al., 1978 | | | | | + |
| Bland et al., 1978 | | + | | | + |
| Kasuga et al., 1979 | + | | + | | |
| Tager et al., 1979 | | - | | - | - |
| Speizer et al., 1980 | | | | - | + |
| Weiss et al., 1980 | | - | + | | |
| Bonham & Wilson, 1981[2] | | | | | + |
| Dodge, 1982 | - | + | + | | + |
| Gortmaker et al., 1982[2] | + | | | + | - |
| Ekwo et al., 1983 | | + | | | |
| Rantakallio, 1983 | | | | | + |
| Schenker et al., 1983 | - | - | - | | +,- |
| Charlton, 1984 | | + | | | |
| Lebowitz, 1984 | | | | | - |
| Tashkin et al., 1984 | | - | - | | - |
| Vogt, 1984[2] | | | | | - |
| Ware et al., 1984 | | + | + | - | + |
| Fergusson & Horwood, 1985 | - | | - | - | |
| Horwood et al., 1985 | - | | | | |
| Spinaci et al., 1985 | | + | | | + |
| Burchfiel et al., 1986 | +[4] | - | + | +[3] | +,+[4] |
| McConnochie & Roghmann, 1986a | - | | +,-[5] | | |
| Park & Kim, 1986, 1988 | | - | | | |
| Strachan & Elton, 1986 | | - | - | | - |
| Teculescu et al., 1986 | | - | | | + |
| Willat, 1986[2] | | | | | + |
| O'Connor et al., 1987 | | | | | - |
| Stern et al., 1987, 1989 | +,-[6] | + | - | - | +,- |
| Tsimoyianis et al., 1987 | - | - | - | - | - |
| Andrae et al., 1988[2] | +,-[7] | + | | | - |
| Dijkstra et al., 1988 | - | - | | | + |
| Moreno et al., 1988 | | | - | | |
| Somerville et al., 1988 | - | + | + | +[3] | |
| Angioni et al., 1989 | - | | - | | +,-[8] |
| Berwick et al., 1989 | | | | | - |
| Chan et al., 1989b | | +[9] | +,-[10] | | |
| McConnochie & Roghmann, 1989 | - | | + | | |
| Neuspeil et al., 1989 | - | | - | + | |
| Sherman et al., 1990 | - | | | | |
| Strachan et al., 1990[11] | | - | - | | + |
| Summary: | | | | | |
| plus:minus for all studies | 5:16 | 11:13 | 10:13 | 4:8 | 18:15 |

(Revised and updated from Witorsch, 1990)

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Table II continued:

[1]A "+" indicates that a statistically significant effect ($p \leq 0.05$) was reported, a "-" indicates that a statistically significant effect was looked for but not found.
[2]Preschool children were included in study population.
[3]Effect reported for girls only.
[4]Effect reported for boys only.
[5]Positive only for children with a family history of respiratory allergy; negative in children with no such history.
[6]Ever had asthma, had doctor-diagnosed asthma in the previous year.
[7]Positive only for children living in damp homes; negative for all others.
[8]Positive for allergy in children of allergic parents; negative for all others.
[9]In low birth weight children only.
[10]Positive for daytime (but not nocturnal) cough in normal birth weight children; negative in low birth weight children.
[11]Employed salivary cotinine as a marker for ETS exposure.

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Table III. Parental Smoking and Middle Ear Disease in Children

| Study | Significance[1] | Symptoms or illness (age in yrs/No. of subjects) |
|---|---|---|
| Kraemer et al., 1983 | + | middle ear effusion (ages not given/152) |
| Marchisio et al., 1884[a] | - | middle ear effusion (5 mos-12 yr/172) |
| Pukander and Karma, 1984[a] | - | middle ear effusion (7-29 mos/753) |
| Rockley, 1984[a] | - | chronic serous otitis media (4-14/78) |
| Van Cauwenberge & Kluyskens, 1984[a] | - | middle ear effusion (2.5-6/2069) |
| Black, 1985 | + | serous otitis media (4-9/442) |
| Iversen et al., 1985 | + | middle ear effusion ($\leq$ 7/337) |
| Pukander et al., 1985 | + | acute otitis media (2-3/471) |
| Fleming et al., 1987 | - | otitis media (<5/575) |
| Kallail et al., 1987 | - | middle ear "problems" (6-10 or 11/238)[2] |
| Reed & Lutz, 1988 | + | middle ear effusion (ages not given/45) |
| Zielhuis et al., 1988[a] | - | middle ear effusion (3/< 1439) |
| Hinton, 1989 | - | surgery for otitis media with effusion (1-12/151) |
| Strachan et al., 1989 | + | middle ear effusion (6.5-7.5/736) |
| Ross et al., 1990[a] | - | acute otitis media (3-5/297) |
| Strachan, 1990[a] | - | type B tympanogram (middle ear effusion; type C tympanogram (underpressure) (6.5-7.5/872) |
| Strachan et al., 1990[3] | - | "ear trouble" (6.5-7.5/770) |
| SUMMARY:[4] | 6:11 | |

[1] + = Significantly different from non-ETS exposed ($p \leq 0.05$); - = Not different from non-ETS exposed ($p > 0.05$).
[2] Estimated (the exact range of ages was impossible to determine from the information presented).
[3] Employed salivary cotinine as a marker for ETS exposure.
[4] Plus:minus for all studies.
[a] Not reviewed by NRC (1986), Surgeon General (1986), or the current EPA risk assessment (U.S. EPA, 1990).

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Table IV. Studies of Parental Smoking and Pulmonary Function in Children

| | Published Study | Source of Subjects | No. of Subjects (ages)[a] |
|---|---|---|---|
| 1. | Leeder et al., 1976b | London, England | 454 (5) |
| 2. | Schilling et al., 1977 | Three U.S. cities | 816 (7-18) |
| 3. | Yarnell & St. Leger, 1979 | Cardiff, Wales | 214 (7-11) |
| 4. | Tager et al., 1976 | East Boston, MA | 140 (5-31) |
| 5. | Tager et al., 1979 | East Boston, MA | 261 (5-19) |
| 6. | Weiss et al., 1980 | East Boston, MA | 238 (5-10) |
| 7. | Tager et al., 1983[b] | East Boston, MA | 715 (4-28) |
| 8. | Tager et al., 1985[b] | East Boston, MA | 669 (5-19) |
| 9. | O'Connor et al., 1987 | East Boston, MA | 265[c] (6-21) |
| 10. | Speizer et al., 1980 | Six U.S. cities | 5842 (6-10) |
| 11. | Ware et al., 1984 | Six U.S. cities | 7112 (6-9) |
| 12. | Berkey et al., 1986[b] | Six U.S. Cities | 7834 (6-10) |
| 13. | Hasselblad et al., 1981 | Seven U.S. areas | 16689 (6-13) |
| 14. | Dodge, 1982[b] | Three Arizona towns | 472 (8-12) |
| 15. | Ekwo et al., 1983 | Iowa City, IA | 183 (6-12) |
| 16. | Lebowitz et al., 1982 | Tucson, AZ | 271 ($\geq$ 6) |
| 17. | Lebowitz, 1984 | Tucson, AZ | 24 (4-24) |
| 18. | Lebowitz et al., 1984 | Tucson, AZ | 271 (13.5)[d] |
| 19. | Lebowitz et al., 1987[b] | Tucson, AZ | 353 (5.5-25) |
| 20. | Lebowitz & Holberg, 1987[b] | Tucson, AZ | 362 (5.5-25) |
| 21. | Tashkin et al., 1984 | Los Angeles, CA | 971 (7-17) |
| 22. | Vedal et al., 1984 | Western Pennsylvania | 3175 (5-14) |
| 23. | Spinaci et al., 1985 | Turin, Italy | 2385 (11)[d] |
| 24. | Burchfiel et al., 1986 | Tecumseh, MI | 1315 (10-19) |
| 25. | Chen and Li, 1986 | Shanghai, China | 571 (8-16) |
| 26. | Murray & Morrison, 1986 | Vancouver, BC, Canada | 94 (7-17)[e] |
| 27. | Teculescu et al., 1986 | Vandouvre, France | 92 (10-16) |
| 28. | Evans et al., 1987 | New York, NY | 276 (4-17)[e] |
| 29. | Stern et al., 1987, 1989 | Ten Canadian towns | 3336 (7-12)[f] |
| 30. | Tsimoyianis et al., 1987 | Nassau County, NY | 193 (12-17) |
| 31. | Dijkstra et al., 1988[b] | Netherlands | 632 (6-12) |
| 32. | Martinez et al., 1988 | Viterbo, Italy | 166 (9)[g] |
| 33. | Masi et al., 1988 | Montreal, Canada | <293 (14-17) |
| 34. | Murray & Morrison, 1988 | Vancouver, BC, Canada | 240 (7-17)[e] |
| 35. | Chan et al., 1989a | London, England | 250 (7) |
| 36. | Kauffmann et al., 1989 | Seven French cities | 1160 (6-10) |
| 37. | Murray & Morrison, 1989 | Vancouver, BC, Canada | 293/285[h] (6-17) |
| 38. | Strachan et al., 1990 | Edinburgh, Scotland | 770 (7) |

(Revised and updated from Witorsch, 1990)
[a] Ages are in years.
[b] Longitudinal study; all others are cross-sectional.
[c] Plus 21 asthmatic children, analyzed separately.

Table IV continued:

[d]Mean age.
[e]All children in this study were asthmatics.
[f]Includes approximately 255 asthmatic children.
[g]Includes 17 asthmatic children.
[h]Evaluated for effect of smoking mother/evaluated for effect of smoking father. All children in this study were asthmatics.

Table V. Results of Studies on Parental Smoking and Pulmonary Function in Nonasthmatic Children

| Study | $FEV_1$ or $FEV_{0.75}$ | $FEF_{25-75}$ | FVC | Vmax[1] | PEFR |
|---|---|---|---|---|---|
| 1. | | | | NC[2] | |
| 2. | NC | | NC | decr.[2,3] | NC |
| 3. | decr. 3%[3,4] | decr. 13%[3,4] | NC | | |
| 4. | decr.[4,5] | | | | |
| 5. | NC | "decr."[6] | | | |
| 6. | NC | decr.[4] | | | |
| 7. | decr. 7%[4] | NC | | | |
| 8. | decr.[4] | decr.[4] | | | |
| 9. | decr. 5-7%[4] | decr. 14-15%[4] | NC | | |
| 10. | NC | | incr. | | |
| 11. | decr. 0.6-0.9%[4] | | incr. | | |
| 12. | decr. 0.81%[4] | | NC | | |
| 13. | decr. 0.7-1.6%[4] | | | | |
| 14. | NC | | | | |
| 15. | NC | NC | NC | NC | NC |
| 16. | NC | | NC | NC | |
| 17. | | | | NC | |
| 18. | NC | | NC | NC | |
| 19. | NC | | incr. | NC | |
| 20. | NC | | incr. | NC | |
| 21. | NC | decr. 2.5%[3,4] | NC | decr. | |
| 22. | NC | decr. 4%[3,4] | incr. | | |
| 23. | decr. | NC | NC | NC | |
| 24. | decr. 4.6%[5] | | decr. 4.9%[5] | | decr. 5.1%[3] |
| 25. | decr. 3%[3,7] | decr. 6%[3,7] | NC | | |
| 27. | decr. 5%[5] | | NC | decr.[5] | |
| 29.[8] | decr. 1.07% | | NC | | |
| 30. | | NC | | | |
| 31. | decr. 1.8%[9,10] | decr. 5.3%[9,10] | NC | | decr. 3.3% |
| 32.[11] | NC | | | | |
| 33. | NC | decr.[5] | NC | | NC |
| 36. | decr.[4] | decr.[4] | NC | | |
| 35. | NC[12] | | | | |
| 38. | NC[13] | NC | NC | | NC |
| SUMMARY: | 15:16[14] | 11:5 | 6:16 | 3:8 | 2:4 |

(Revised and updated from Witorsch, 1990)
Numbers in the first column correspond to studies listed in Table IV.
[1] $Vmax_{50}$ or $Vmax_{75}$.
[2] NC = No statistically significant change; decr. = statistically significant decrease.
[3] Seen in females only.
[4] Associated mainly or entirely with maternal smoking.
[5] Seen in males only.

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Table V continued:

[6]Statistically significant difference only for trend test among children with 0, 1, or 2 smoking parents and only when smoking children and their sibs are included.
[7]Associated with paternal smoking.
[8]Includes asthmatic children.
[9]Associated with total household ETS exposure.
[10]Significant effect seen with cross-sectional analysis of the data, but not with longitudinal analysis.
[11]Includes 17 asthmatic children.
[12]Reported for 7-year-old children who had low birth weights (under 200 g). Other pulmonary function parameters (e.g., FVC, PEFR, Vmax$_{50}$, or Vmax75) also measured in reference (normal birth weight) as well as low birth weight children. These data, however, were unreported.
[13]Employed salivary cotinine as a marker for ETS exposure.
[14]No. reporting decrease or increase:No. reporting NC.

Table VI. Results of Studies on Parental Smoking and Pulmonary Function in Asthmatic Children

| Study | $FEV_1$ or $FEV_{0.75}$ | $FEF_{25-75}$ | FVC | PEFR |
|---|---|---|---|---|
| 9. | NC | NC | NC | |
| 26. | decr. 13%[1] | decr. 23%[1] | decr. 12.3%[1] | |
| 28. | NC | NC | | NC |
| 34[2] | decr. 12% | decr. 19% | | |
| 34[3] | NC | NC | | |
| 37.[4] | decr. 7% | decr. 12% | decr. 4% | |
| 37.[5] | decr. 9% | decr. 13% | NC | |
| 37.[6] | NC | NC | NC | |
| 37. | decr.[7] | decr.[7] | NC | |
| SUMMARY:[8] | 5:4 | 5:4 | 2:4 | 0:1 |

Numbers in the first column correspond to studies listed in Table IV; none of the studies involving asthmatics reported Vmax values.

[1]Associated with maternal smoking.
[2]In the "cold, wet season" (October-May).
[3]In the "warm, dry season" (June-September).
[4]Both sexes together, tested for separate effect of smoking mother or smoking father.
[5]Boys only, tested for effect of smoking mother.
[6]Girls only, tested for effect of smoking mother.
[7]Both sexes together and grouped by age, tested for effect of smoking mother. Effect seen in children aged 12-17 yrs, but not in those 7-11 or < 7 years of age.
[8]No. reporting decrease:No. reporting NC.

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Table VII. Results of Concurrent Tests of $FEV_1$ or $FEV_{0.75}$ and $FEF_{25-75}$ in Studies on Parental Smoking and Pulmonary Function in Nonasthmatic Children

| Published Study | $FEV_1$ or $FEV_{0.75}$ | $FEF_{25-75}$ |
|---|---|---|
| Yarnell & St. Leger, 1979 | decr. 3%[1] | decr. 13%[1] |
| Tager et al., 1979 | NC | "decr."[2] |
| Weiss et al., 1980 | NC | decr.[3] |
| Tager et al., 1983 | decr. 7%[3] | NC |
| Tager et al., 1985 | decr.[3] | decr.[3] |
| O'Connor et al., 1987[4] | decr. 5-7%[3] | decr. 14-15%[3] |
| Ekwo et al., 1983 | NC | NC |
| Tashkin et al., 1984 | NC | decr. 2.5%[1] |
| Vedal et al., 1984 | NC | decr. 4%[1] |
| Spinaci et al., 1985 | decr.[3] | NC |
| Tager et al., 1985 | decr.[3] | decr.[3] |
| Chen & Li, 1986 | decr. 3%[5] | decr. 6%[5] |
| Dijkstra et al., 1988 | decr. 1.8%[6] | decr. 5.3%[6] |
| Masi et al., 1988 | NC | decr.[7] |
| Kauffmann et al., 1989 | decr.[3] | decr.[3] |
| Strachan et al., 1990[8] | NC | NC |

(Revised and updated from Witorsch, 1990)

[1]Girls only, tested for effect of smoking mother.
[2]Statistically significant difference only for trend test among children with 0, 1, or 2 smoking parents and only when smoking children and their siblings are included.
[3]Associated mainly or entirely with maternal smoking.
[4]Nonasthmatic children only.
[5]Associated with paternal smoking (no mothers were said to be smokers) and seen in female children only.
[6]Associated with total household ETS exposure; significant effect seen with cross-sectional (but not longitudinal) analysis of the data.
[7]Seen in boys only.
[8]Employed salivary cotinine as a marker for ETS exposure.

Table VIII. Results of Studies on Parental Smoking and Pulmonary Function in Children - Comparisons within the Same Cohorts

| Source & Study Number | $FEV_1$ or $FEV_{0.75}$ | $FEF_{25-75}$ | FVC | Vmax[1] | PEFR |
|---|---|---|---|---|---|
| **East Boston, MA:** | | | | | |
| 4. | decr.[2,3] | | | | |
| 5. | NC[4] | "decr."[5] | | | |
| 6. | NC | decr.[2] | | | |
| 7. | decr. 7%[2] | NC | | | |
| 8. | decr.[4] | decr.[4] | | | |
| 9. | decr. 5-7%[2] | decr. 14-15%[2] | NC | | |
| **Six U.S. cities:** | | | | | |
| 10. | NC | | incr. | | |
| 11. | decr. 0.6-0.9%[2] | | incr. | | |
| 12. | decr. 0.85% | | NC | | |
| **Tucson, AZ:** | | | | | |
| 16. | NC | | NC | | NC |
| 17. | | | | | NC |
| 18. | NC | | NC | NC | |
| 19. | NC | | incr. | NC | |

(Revised from Witorsch, 1990)
Numbers in the first column correspond to studies listed in Table III.

[1] $Vmax_{50}$ or $Vmax_{75}$.
[2] Associated mainly or entirely with maternal smoking.
[3] Seen in males only.
[4] NC = No change.
[5] Statistically significant difference only for trend test among children with 0, 1, or 2 smoking parents and only when smoking children and their siblings are included.

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## VII. APPENDIX--SPECIFIC EXAMPLES

In this Appendix, we present specific examples supporting our critique of the draft EPA document:

### Incompleteness

a. In the section entitled, "RECENT EPIDEMIOLOGIC EVIDENCE" (pp. 5-5 to 5-9 including Table 5-1), the epidemiologic literature since the NRC and Surgeon General's 1986 Reports relating parental or household smoking (ETS) to pulmonary function and respiratory symptoms and disease in children is listed.

Table 5-1 is poorly organized, as it groups together studies on health effects (symptoms and disease) in infants and older children as well as functional studies. A preferable arrangement of the studies would have been a separate listing of symptoms and illness in pre-school children, a separate listing of similar studies in school-age children, and a separate listing of pulmonary function studies. The listing in Table 5-1 is by no means complete. For comparison, see Tables I, II, and IV (in Section V of this critique), which include most if not all studies included in or published subsequent to the 1986 Reports, as well as some not reviewed in 1986.

The legend associated with Table 5-1 is also of concern. It indicates that this is a listing of "selected" studies subsequent to the 1986 reports, yet the basis of this selectivity is not indicated.

b. Section 5.6.3, p. 5-29 to 5-32, which discusses Recent Studies on Pulmonary function, is incomplete; compare with Table IV in Section V of this critique.

c. p. 5-33 to 5-34, review of literature on middle ear effusion: This review of the literature is incomplete. For comparison see our Table III, which shows that the association between parental smoking and middle ear effusion is inconsistent.

### Superficiality

1) 5-4.1., p. 5-9: Portions of this section are verbatim from page 48 of the original Surgeon General's (1986) report (without appropriate indication of quotation).

2) 5-4.2, p. 5-11 to 5-12: Several passages of this section are almost verbatim copies of sections in the original NRC (1986) report (without appropriate indication of quotation), e.g., par. 2, p. 5-11 contain passages from page 190 of the NRC report.

3) p. 5-12, par. at bottom to top of p. 5-13.: "It seems unlikely, however, that parental perceptions of their children's health are sufficiently distorted or influenced by their own health conditions to have a broad-based influence across numerous studies." This statement is unattributed and rather arbitrary. It is also inconsistent with available data and prevailing informed opinion. Furthermore, there is no rule that the same confounding factor influences an association in every study. A variety of confounders (e.g., recall bias, socioeconomic status, and active smoking in children) could act independently or interdependently to affect the outcome of an epidemiologic study.

4) 5.5.1, p. 5-20: This summary of the SGs conclusion is almost a copy of passages from the original report (without indication of quotation). The first paragraph can be found in p. 44 of the SG report, while some of the second is found on p. 38 of the report.

5) 5.5.2, p. 5-21: Portions of this section are very similar to p. 208 of the NRC report.

6) 5.6.1., p. 5-27: Passages here correspond to those of p. 49 of the SG report, without indication of quotation (see p. 49 of the SG report).

7) 5.6.2, p. 5-28: Sections of the first paragraph can be seen on page 194 of the NRC (1986) report ("Nevertheless . . .").

b. p. 5-12, l. 4-5: "Furthermore, there appears to be a dose-response relationship between exposure and the likelihood of the child's developing respiratory symptoms or a respiratory illness."

This statement is an oversimplification of a complex concept. A quantitative relationship between the amount of parental smoking (or number of household smokers) and adverse respiratory health effects may be a consequence of ETS exposure--but alternate, unrefuted, explanations also exist. Confounders can affect a relationship in a quantitative sense. The amount of active smoking in children, for example, could parallel the amount of parental smoking. Furthermore, parental smoking may be increased in situations where the health of the child could be adversely affected indirectly by nonspecific living conditions, as in lower socioeconomic groups, with increased air pollution, or with more stress.

c. p. 5-13, par. 2: Statements regarding the paper of Stern et. al. (1987).

This paper was presented at the Indoor Air Conference in Berlin (August, 1987) and was not peer reviewed. The same data were recently published in a peer reviewed journal (Stern et al., 1989).

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The account in the EPA report is inaccurate, possibly because the Berlin transcript had some points of confusion that were later clarified in the peer reviewed paper. For example, the independent variable was smoking during pregnancy and (not or) postnatally. The authors reported a statistically significant effect on cough (OR = 1.45) but not on phlegm or wheeze (Their findings on respiratory illness and pulmonary function and related issues will be discussed later, as appropriate).

The following aspects of this paper were not noted in the EPA report: 1) clinical data lacked verification; 2) ETS exposure lacked verification; 3) details of how confounders (parental education, parental illness history, and gas cooking in the home) were considered are lacking.

The independent variable in this study was smoking during pregnancy and during the first 2 years of life, which does not exclude the possibility that in utero effects could have contributed to these associations.

d. p. 5-13, bottom to p. 5-14 top: Statements regarding paper by Marks (1988).

This is a letter to the editor and provides no data and little description of methodology. Therefore, it is impossible to evaluate this study, and it probably does not warrant discussion in the document.

e. p. 5-14, l. 3-10: Statements regarding the study of Somerville et al. (1988).

The following shortcomings in this paper should have been noted: 1) lack of ETS verification, 2) lack of symptom/illness verification clinically, and 3) omission of a variety of important confounders (indoor air quality, outdoor air quality, active smoking in children, smoke of others in the household). The dose-response they report (Table 5) is not compelling.

The last sentence of this paragraph ("'Frequent' cough first thing . . .") suggests the tendency for the authors of the EPA report to dismiss statistical criteria when it conflicts with their position. This is discussed in more detail in Section 4 below.

f. P. 5-14, line 11-15: Statements regarding the study of McConnochie and Roghmann (1986).

In addition to noting the usual inadequacies (e.g., ETS exposure validation) and/or strengths (validation of clinical data), it should be noted that in this study maternal smoking (or household smoking) was not a risk factor for wheeze in the absence of family history of allergy, suggesting that genetic predisposition may be an important factor. Other potentially

important confounding variables for wheeze noted in this study were artificial feeding postnatally and offspring gender. These confounders usually are not considered and point to the complexity of the problems the investigator encounters in epidemiologic papers relating to the reported effects of maternal smoking.

The McConnochie and Roghmann (1989) report of an association between maternal smoking and wheezing at age 13 is not consistent with the results of a more recent study by Sherman et al. (1990), which failed to demonstrate an association of asthma with either maternal or paternal smoking. Furthermore, McConnochie and Roghmann (1989) do not appear to adequately take into account the potential confounding effect of active smoking by children, which may be significant in the age group of the subjects they studied.

g. p. 5-14, l. 15-25: Statements pertaining to the study of Chan et al. (1989b).

In this study, effects of maternal smoking on respiratory symptoms in 7-year-old low-birth-weight children (under 2000 g) at birth were compared with a reference group of 7-year-olds of normal birth weight. The EPA document neglected to mention that in the reference group, the maternal smoking effect on wheeze was not statistically significant, although a significant association was observed between smoking and daytime, but not nocturnal, cough. In the low-birth-weight group, there was a statistically significant association between smoking and wheeze (but not cough) that withstood multiple logistic regression (allowing for family history of wheeze, atopic skin test, low SES, neonatal oxygen score [level of neonatal intensive treatment]). It does not appear, however, that the association between maternal smoking and daytime cough in the reference group was subject to multiple logistic regression.

The following aspects of this study should have been noted: (1) lack of clinical verification, (2) lack of ETS exposure verification, and (3) relatively crude socioeconomic status correction. Finally, since low birth weight has been reported to be associated with smoking during pregnancy, the association reported herein could reflect an effect of such smoking (a possibility acknowledged by the authors of the paper) rather than of ETS.

h. p. 5-17, par 2: "Some additional precautions . . ."

This paragraph deals with the issue of active smoking in children. The statement that "most researchers have been aware of the potential confounding effect of smoking and have attempted to control for it" is an oversimplification of a very complex situation. As discussed previously, the issue of active smoking in children may be rather complex and could account for much of the variability in the studies on health effects of ETS in older children (see Section III above).

i. p. 5-18, l. 4 to 11: "In conclusion there is no apparent single source of systematic bias that might explain . . . through the adolescent years."

Since a plethora of confounders affect respiratory health in children, a "single source of bias" would be unlikely, and to expect one is naive. Family history is only one of many factors (e.g., SES, active smoking in children, environmental factors, etc.) that can affect the outcome of such studies. The statement that it "is reasonable to conclude that parental smoking increases the incidence of respiratory symptoms from infancy well into primary school years and probably through adolescent years" is not supportable, especially as it pertains to symptoms in older children.

j. p. 5-22 bottom: Statements pertaining to the study of Ogston et al. (1987).

The EPA report failed to take into account the alternate considerations in this study. The fact that alimentary illness in infants (diarrhea, vomiting, colic), in addition to respiratory disease, has been associated with parental smoking could suggest that the association of respiratory illness with ETS is nonspecific. In this regard, it is noteworthy that both respiratory and alimentary illness appeared to be influenced by the same factors (maternal age, bottle feeding, and fathers' social class).

k. P. 5-29, par. 3: Statements pertaining to the study of Kauffmann et al. (1989).

This is an extension of previous French PAARC studies on the effects of spousal smoking on pulmonary function and respiratory health effects in adults. ETS exposure is assumed (without verification) to result from parental smoking and is, therefore, subject to misclassification error. Although the association between the level of parental education and pulmonary function was examined, it is uncertain whether this potential confounder (or any other potentially influential co-variables) were adjusted for in the analysis relating to maternal smoking. Furthermore, parental education probably is a relatively weak estimate of socioeconomic status. In other words, this study did not appear to establish that maternal smoking independently caused a decrement in pulmonary function in children.

l. p. 5-29, par. 3, to p. 5-30, top: Statements pertaining to the study of Masi et al. (1988).

Since ETS exposure was assumed on the basis of responses on mail-in questionnaires, without verification, this study is subject to misclassification error. The subject was the respondent who had to provide exposure information on up to seven periods in his/her life. From this information, the following

estimates of lifetime exposure were calculated: person x years (home) and packs/day x years (work). Thus the estimates of exposure may have been subject to significant recall bias, as well as imprecision. The confounders considered in this analysis were cooking fuels and "respiratory pressures." No adjustment was made for socioeconomic status.

This study showed an effect of ETS exposure in the home on $FEF_{25-75}$ in male nonasthmatic children. To our knowledge, no other report shows effects on FEF $_{25-75}$ in males only (see Table V, Section V). In females, an effect was not seen on flow parameters ($FEV_1$ or $FEF_{25-75}$), but a difference in diffusing capacity was reported. This effect was associated with work exposure and not home exposure. The apparent sexual dichotomy was evident, even though the estimates of exposure at home and at work were similar for males and females. The data appear to be spurious, of questionable plausibility, and are inconsistent with other reports in the literature.

m. p. 5-30, first full paragraph: Statements pertaining to the study of Lebowitz et al. (1987) and Lebowitz and Holberg (1987).

This study lacked verification of ETS exposure and, hence, was subject to misclassification error. The only association found with parental smoking was a significant decrease in size compensated flow, $Vmax_{50}/FVC$, with an increase in FVC. No independent association with maternal smoking was found for $FEV_1$ (considered the most reliable indicator of pulmonary function) or $Vmax_{50}$. These data add additional variation to the already highly inconsistent pulmonary function data (e.g., $FEV_1$, $Vmax_{50}$, FVC) in studies attempting to relate parental smoking to pulmonary function. The authors of the study concluded "The effects of parental smoking are somewhat inconsistent; in some cases a maternal smoking effect is noted only within other risk factor subgroups" (Lebowitz et al., 1987).

Furthermore, the longitudinal component of this study failed to confirm the two studies that report an association between parental smoking and lung growth (Tager et al., 1983; Berkey et al., 1986). As discussed in Section III, five longitudinal studies have attempted to relate parental smoking to changes in lung growth in children. While two have reported an association, three others have failed to do so (Lebowitz et al., 1987; Dodge, 1982; Dijkstra et al., 1988). Both Tager et al. (1987) and Lebowitz and Holberg (1988) have attempted to reconcile differences in the findings of their longitudinal studies. Among the possible reasons for differences in the two outcomes are confounding variables (e.g., different climates in the two studies). This again illustrates the complexity of considering confounding variables.

n. P. 5-30, par. 2: Statements regarding the studies of Stern et al. (1987) and Teculescu et al. (1986).

As mentioned earlier, the pulmonary function data of Stern et al.(1987) were published in revised form (Stern et al., 1989. The only decrement reported in the revised version is a 1.07% decrement in $FEV_1$ of 7-12 year old children exposed to maternal smoking during pregnancy and the first two years of life, with no change in FVC. The authors state a level of statistical significance but provide no data (e.g., standard errors or 95% confidence limits) on pulmonary function as it applies to parental smoking. In another part of the paper (relating early hospitalization to risk in later life), more comprehensive pulmonary function data are presented (percent decline in FVC, $FEV_1$, PEF, $FEF_{25-75}$, with 95% confidence limits). In light of the completeness of these data, it is provocative as to why the data are so superficially presented as they relate to maternal smoking. A 1% decrement is quite small, still well within the range of normal pulmonary function, and of very questionable clinical or even physiological significance. Furthermore, since this study failed to distinguish smoking during pregnancy from parental postnatal smoking, one cannot rule out the possibility that the small decrement represents an in utero effect.

Teculescu et al. (1986) reported that the observed $FEV_1$ of children of nonsmoking parents was $107 \pm 12\%$ of the predicted value, while the value for children with two smoking parents was $102 \pm 10\%$ of that predicted, and that the difference was statistically significant ($p < 0.05$). They also reported statistically significant differences in predicted $FEF_{50}$ ($107\% \pm 25\%$ of predicted in children of nonsmoking parents vs. $97 \pm 18\%$ of predicted for children with smoking parents). No other statistically significant changes were observed (e.g., FVC, $FEV_1/VC$, $FEF_{25}$). None of the data were corrected for potential confounders. These data reveal that even when parents smoke, the parameters of their children's lung function are not statistically significantly different from normal (i.e., 100% of predicted values). When the data were compared on a gender basis, no statistically significant effect was found for girls, only for boys. It is noteworthy that although some studies report gender-specific effects, there does not appear, as yet, to be a consistent pattern (see Tables V and VI, Section III).

o. p. 5-35: Statements pertaining to the study of Fleming et al. (1987).

The main observation of this study is that day care is a risk factor for upper respiratory and ear infections in preschoolers. Maternal smoking failed to increase the risk of the latter, while increasing the risk of the former. Among the concerns with regard to this paper are: 1) clinical verification of symptoms is lacking, 2) verification of maternal smoking is lacking, 3) extent of confounders influencing maternal smoking effect seems very limited. This study is important because it presents a new confounding variable, day care, which has not been considered in most other studies to date.

p. p. 5-35: Statements pertaining to the study of Willat et al (1986).

This is a study involving 93 subjects undergoing tonsillectomy and 61 controls. However, for the sore throat effect, this group was considered as a single population. The imbalance in the population may have confounded the outcome of the study. The fact that the association between maternal smoking and sore throat was stronger in younger children (under 6.9 yrs), although inconsistent with the effect of active smoking in children, may reflect the involvement of confounders usually associated with parental smoking in young children (as discussed in Section III above).

q. p. 5-36: Statements pertaining to the study of Chen et al. (1988), in reference to asthma prevalence.

This study reported no statistically significant association between ETS and asthma prevalence in infants. This finding is inconsistent with the prevailing literature linking parental smoking with respiratory diseases in young children. It will be recalled, however, that there were said to be no smoking mothers in this cohort. Perhaps asthma incidence in young children is not an ETS effect but a manifestation of an _in utero_ effect. These workers also found no statistical relationship between household smoking and whooping cough, sinusitis, or measles. The significance of these findings also remains to be determined.

r. p. 5-36: Statements pertaining to the study of Weitzman et al. (1990) in reference to asthma prevalence.

These workers conducted their study in pre-school children, and an association with asthma incidence, medication, and age of onset is consistent with the literature suggesting a link between maternal smoking and respiratory disease in this age group (although at variance with the data of Chen et al., 1988, in the preceding paragraph). Several aspects of this paper should have been noted in the EPA analysis. Among the confounders not considered was family history of asthma, which appears to be a strong risk factor. There also was a reported association between maternal smoking and number of hospitalizations among nonasthmatic children; this could be a reflection of parental neglect rather than an effect of ETS.

s. p. 5-36: Statements pertaining to the study of Martinez et al. (1988) in reference to asthma prevalence.

Several aspects of this study were not noted in the EPA report. ETS exposure was not validated. Active smoking in children was not considered. Asthma was not clinically verified. Certain confounders were not considered (such as SES and climate). No maternal smoking effect was observed on baseline $FEV_1$ in either the control or asthmatic subjects, adding to the

already inconsistent data on the issue of the possible relationship between parental smoking and baseline pulmonary function. The fact that this group reported an association between maternal smoking and bronchial responsiveness in nonasthmatics conflicts with several other studies (O'Connor et al., 1987; Weiss et al., 1985; Corbo et al., 1989). On the other hand, several groups have reported increased bronchial responsiveness in asthmatic children of maternal smokers (O'Connor et al., 1987; Murray and Morrison, 1986). This raises the possibility of some effect of maternal smoking in a particular subgroup, but the mechanism of this effect (genetic, psychogenic, or other factors, or ETS) remains to be determined. The link proposed in this study between ETS exposure, gender, and the immune response is highly speculative. The analysis of Stankus and co-workers in adults, for example, shows no association between tobacco smoke "sensitivity" and immunologic reactivity to tobacco antigens (by skin test or serology) (Stankus et al., 1988).

t. p. 5-37: Reference to the study of Geller-Bernstein et al. (1987) with regard to asthma prevalence.

This study, which showed no correlation between IgE levels and ETS exposure, is inconsistent with the hypothesis proposed by Martinez et al. (1988). In the Geller-Bernstein et al. study, parental smoking was neither described in the protocol nor specified. This study apparently lacked consideration of important confounders. However, it also suggests that artificial feeding is an important variable to be considered in epidemiologic studies. Maternal smoking has also been reported to influence the duration of nursing behavior and hormonal control of lactation (Andersen et al., 1982), so this introduces a new indirect confounding variable

u. p. 5-38, par. 1: Discussion of studies of Murray and Morrison (1986, 1989) in reference to asthmatic symptoms:

These studies lack verification of ETS exposure. Attention to confounding variables was fairly thorough, although not comprehensive. The lack of effect the authors reported in young children (aged 1-7) is not consistent with the association between maternal smoking and respiratory effects in young children reported in other studies. The association reported between maternal smoking in boys and asthmatic symptoms and functional deficits as they age seems unusual. One would expect that boys spend less time with their mothers (and at home) as they get older. Among the factors to considered are unreported active smoking in older boys, occupational exposures, or exposures through hobbies.

v. p. 5-38, par. 2: Discussion of studies of Evans et al. (1987), par. 2.

The lack of association between household smoking and pulmonary function decrement in asthmatics observed here is inconsistent with the findings of Murray and Morrison (1986, 1989). The increased emergency room visits associated with such exposures, in the absence of other associations, also seem unusual. It may either reflect a spurious observation or some as yet unexplained variable (such as anxiety on the part of the parent).

q. p. 5-39: Discussion of nonspecific ailments.

Since the two studies reviewed here (Ostro, 1988; Charlton and Blair, 1989) pertain to nonspecific ailments (e.g., disability days, absenteeism), they could reflect an indirect lifestyle factor, such as socioeconomic status or parental neglect.

<u>Inaccuracies</u>

a. p. 5-2, l. 11-14: "A large study by Chen et al. (1988) has found increased respiratory illness in infants of nonsmoking mothers with ETS exposure from other household smokers after birth. This somewhat discounts the role of the potential confounding effect of <u>in utero</u> exposure to tobacco products from the mother's smoking during pregnancy."

In the absence of adequate verification of maternal smoking status, it is an overstatement to interpret this study as discounting a role for <u>in utero</u> exposures, especially in view of other studies that tend to suggest that <u>in utero</u> exposure may be important (e.g., Stern et al., 1987, 1989; Taylor and Wadsworth, 1987).

There are three studies by Chen and associates on household smoking where presumably the mother does not smoke. Although these studies are fairly well done (relative to most of the studies in the field), they cannot exclude factors such as undercorrection for socioeconomic status (e.g., parental neglect, outdoor air quality), some yet unidentified variable associated with household (usually paternal) smoking, recall bias, or transmission of infection from parents or other household members to the child.

b. Section 5.2 entitled "EXPOSURE OF CHILDREN" (p. 5-3 and 5-4).

The report alludes to studies that have reported that children of smoking parents have increased levels of the tobacco marker, cotinine, in their body fluids, and that these levels vary in relation to the degree of ETS exposure (e.g., number of household smokers, etc.). This implies that even though most pulmonary function and health effects studies do not verify ETS exposure with a body fluid marker, parental smoking status derived from questionnaires should be a reliable surrogate.

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A survey of these and other relevant studies (Balter et al., 1988; Lee, 1989) reveals, however, that even though body fluid cotinine may be correlated with the presence of the smoking parent, the dose-response relationships are rather imprecise, with large variability within groups and overlap between groups. In other words, uncertainty persists about questionnaire data as a quantitative estimator of ETS exposure.

In the last paragraph on p. 5-4, the EPA report states the following: "There are indications of substantial host-related differences in cotinine concentrations among children, i.e., in experiments with controlled exposure to ETS, cotinine concentrations vary between individuals experiencing the same airborne concentrations of ETS." This is a prudent statement. Recent information about the fate of airborne nicotine from ETS, the uncertainties by which nicotine is absorbed by nonsmokers, and problems associated with nicotine pharmacokinetics, indicate that body fluid cotinine is at best only a semiquantitative estimate of ETS exposure (Lee, 1988; Balter et al., 1988).

c. p. 5-16, par. 1: Statements pertaining to the study of Teculescu et al. (1986).

The description of this paper in the EPA draft report is inaccurate and misleading. This study compared the incidence of chronic cough with sputum and acute respiratory infection in children of nonsmoking parents with children who had two smoking parents. No association was seen for chronic cough, while an apparent increased risk of acute respiratory infection associated with parental smoking was reported. The EPA document neglected to mention that this study lacked correction for confounding variables as well as verification of ETS exposure.

d. p. 5-36, par. 1: Comments pertaining to the report of Stern et al. (1987) in reference to asthma prevalence.

The EPA document is inaccurate in stating that these workers showed an effect on asthma prevalence before the age of two. In actuality, Stern et al. reported that maternal smoking during pregnancy and two years postnatally were associated with increased asthma diagnosis (OR = 1.43) in children at ages 7-12 years. They also reported that maternal smoking did not increase risk of asthma diagnosis in the preceding year. These two findings appear mutually contradictory. It will be recalled that the design of this study is unable to distinguish <u>in utero</u> effects of maternal smoking from postnatal effects.

<u>Lack of objectivity</u>

a. Section 5.3 entitled, "RECENT EPIDEMIOLOGIC EVIDENCE" (pp. 5-5 to 5-9 including Table 5-1).

This section conveys the impression that the recent studies adequately deal (e.g., by use of techniques such as multiple logistic regression) with the potential biases found in previous studies. Among these are: active smoking, parental social class, heating and cooking fuels, parental illness (e.g., cross-infection or genetic predisposition). This is misleading. Usually the studies in question only deal with a select number, not all, of the major confounders that can effect a study's outcome. In addition, the type of correction employed (for example, social class) often is insufficiently rigorous to adjust adequately for the potential confounder.

b. p. 5-11, l. 4-6: "Some studies, including some that have not found a statistically significant increase in the prevalence of respiratory symptoms in ETS-exposed children, observed an increase in prevalence of respiratory symptoms as the number of household smokers increases."

Dismissal of statistical criteria is scientifically inappropriate and suggests either bias or a lack of scientific sophistication.

c. p. 5-11, l. 16-19: "Ferris et al. (1985) have argued, however, that correcting for parental symptoms represents an overcorrection for respiratory symptoms in children since it also corrects for parents' smoking habits."

The implication of this statement, that parental symptoms should not be corrected for in studies because doing so overcorrects for parental smoking, reflects either a bias or naiveté, both of which are scientifically unacceptable. The complication that a confounding variable is closely associated with the major independent variable of interest is not a valid basis for ignoring its significance. As an alternative to ignoring the parental symptomology, a large enough cohort should be examined to ensure adequate numbers of "asymptomatic" smoking parents.

d. p. 5-11, bottom: "In both the Lebowitz and Burrows and Ferris et al. studies, adjustment for parental symptoms or respiratory illness decreased the strength of the apparent association between exposure to ETS and respiratory symptoms but did not eliminate it."

This sentence and the one that follows it are inaccurate and misleading. In actuality, Lebowitz and Burrows found that adjustment for parental respiratory symptoms rendered an association that was previously statistically significant now statistically nonsignificant, a change equivalent to elimination of the association. There are numerous other examples of this in the literature, including those from the work of Ferris and associates (Ware et al., 1984). As in b. above, this statement

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reflects a tendency to use statistical principles (or lack thereof) to support a point of view. Such flexibility in statistical rigor is scientifically inappropriate.

e. p. 5-13, l. 12-17: "Statistical significance . . . not the case for the published studies."

The fact that statistical significance is not always achieved is not to be underestimated, since it represents established rigorous objective criteria. In numerous studies in this field, authors ignore statistical criteria and emphasize trends that are not statistically significant as being meaningful. This tendency is biased and perpetuates misunderstanding. While lack of statistical significance does not discount the possibility of a real association (since it could reflect high variability or inadequate numbers of subjects), studies should be designed so as to obtain less equivocal findings, rather than providing potentially misleading information. In other words, lack of statistical significance should be considered as being consistent with the null hypothesis unless proven otherwise.

The second sentence of this passage suggesting that negative as well as positive associations should be observed if ETS produced no effects is also naive and challengeable. Numerous other factors (such as parental disease, parental recall bias, childhood smoking, socioeconomic status, and in utero effects) could also tend to increase risks. Furthermore, if baseline incidence of a symptom is inherently low in the unexposed population, it would be difficult if not impossible to detect a decrement in such an incidence.

f. p. 5-23, first paragraph: Comments pertaining to the study of Stern et al. (1987).

The description provided in this part of the EPA report is incomplete and misleading. Although these workers report an increased risk of hospitalization in infants for respiratory illness associated with maternal smoking during pregnancy and the first two years of life, they also report (between the ages of 7-12 years) no such association for allergies or certain ailments in the preceding year (diagnosis of asthma, bronchitis, inhalant allergies, or chest illness for three or more days--only incidence of doctor-diagnosed asthma in general was increased in this group). This finding is consistent with the general conclusion of the Surgeon General and NRC reports (1986) that the association between maternal smoking and respiratory disease in children is only consistent in very young children and for the most part diminishes with age.

The next sentence of the EPA draft report (p. 5-23, l. 7, "Moreover . . .") refers to the finding by Stern et al. that children hospitalized in their first two years of life exhibited higher risks of respiratory illness later in life. However, the

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EPA document is inaccurate in its statement and, thus, misleading. The EPA draft document states that "ETS-exposed children" who were hospitalized were at increased risk. In reality, the study reported that all children hospitalized in early life were at increased risk.

g. 5.5.4: Summary and Discussion on Respiratory Illness (p. 5-23 bottom to p. 5-25).

Overall, this section fails to emphasize the fact that although the reported association between ETS and respiratory illness is consistent in young children, the association tends to diminish in strength or disappear as the child ages (as noted in several longitudinal studies, such as Fergusson and Horwood, 1985). The summary also fails to point out the high degree of inconsistency from study to study in school age or older children (as noted in Table II, Section V).

h. p. 5-23 bottom to 5-24 top paragraph.

This section tends to down play the importance of recall bias of illnesses in the relevant epidemiologic studies. In reality, this may be a major problem since the majority of studies, as a rule, base their clinical findings on questionnaire responses without verification. Also, the respondents are frequently called upon to respond to questions for which they have no expertise (e.g., differentiating one symptom or disease from another). In contradiction to the statement on p. 5-24, l. 3, the questions are not very specific and may require considerable subjective judgment.

i. p. 5-24, par. 2: "The consistent association . . ."

This section deals with the issue of whether confounding variables can account for the associations between respiratory illness and parental (usually maternal) smoking. The implication that the effect is attributable to ETS because a single confounding factor would not be operative "over a broad spectrum of countries, cultures, and age groups" is an extreme oversimplification. The confounding factors involved may be varied and complex and may act independently and/or interdependently. As reviewed above, additional factors were pointed out in the studies of Chen, Chan, and McConnochie and Roghmann (e.g., presence and absence of breast feeding, genetic predisposition to respiratory disease, and sex of offspring).

j. p. 5-31, bottom to p. 5-32: Summary and Discussion of Pulmonary Function.

At the outset of this summation the authors appear to attempt to be prudent by noting that when reported, an effect of parental smoking is small and the data are variable. This is evident from our Tables VI and VII.

In the second half of this section, the EPA draft report is less cautious. It cites a paper by Tager et al. indicating that for $FEV_1$ and $FEF_{25-75}$, "some consistency emerges." This is not readily evident from the totality of the data (our Tables V and VI). EPA cites the paper by Masi et al. to suggest that mechanical properties of males are more vulnerable to ETS effects than females. This is also not evident from the totality of the data. Citing the papers of Stern et al. and Masi et al., EPA suggests that ETS exposure in childhood may produce long-term effects on lung function. This is highly speculative and not supported by the data. As indicated earlier, the majority of longitudinal studies do not find an association between parental smoking and lung growth. Finally, since the functional data are so highly inconsistent and indicate that children of parental smokers have pulmonary function within the normal range, it would be prudent to avoid such a speculation at this time.

The concluding statement of this section, that "passive smoking in early childhood is associated with decreased lung function in childhood and with a small reduction in their rate of pulmonary growth and development" is not supported by the data.